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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/461,537 | 12/15/99 | ROYER | J 4216.260-US |

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HM22/0712

EXAMINER

YUC5 I

| ART UNIT | PAPER NUMBER |
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1636

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/461,537

Applicant(s)

ROYER ET AL.

Examiner

Yucel Remy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 December 1999.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *detailed action*.

DETAILED ACTION

Claims 20-22 are pending in the application. This Office action is in response to the amendment filed 15 December 1999 and the Declaration(s) by Wendy T. Yoder filed 16 May 2000.

Priority

This application discloses and claims only subject matter disclosed in prior Application No. 08/816,915, filed March 13, 1997, and names an inventor or inventors named in the prior application. Accordingly, this application may constitute a continuation or division. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. §120 and 37 CFR §1.78. In order to perfect a claim of benefit of a copending application, a reference to the prior application must be inserted as the first sentence of the specification of this application if applicants intend to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included. Applicants are also cautioned that they cannot rely on the filing dates of prior applications 08/269,449, 08/404,678 and 08/726,105 alone because these applications were abandoned prior to the filing date of the present application. In other words, none of the above listed applications were copending with the present application. Therefore, until applicants perfect the claim benefit of priority of application 08/816,915, the effective date accorded the present application is its filing date, December 15, 1999.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Specifically, there are such sequences disclosed at least on pages 3, 7-9, and 11-13. It is also noted that throughout the specification there are SEQ ID. NO. identifiers; however, there is no corresponding sequence listing either on paper or in CRF in the application. Thus, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

As discussed above, this application appears to be a continuation of 08/816,915. If this is the case, the following paragraph or language having the same effect may be used to invoke the procedures of 37 CFR 1.821(e) in which an identical computer readable form from another application is used in a given application. The paragraph should be submitted as a separate paper to be incorporated into the record of the application:

The computer readable form in this application, [insert serial number], is identical with that of Application serial number [insert serial number], filed [insert date]. In accordance with 37 CFR 1.821(e), please use the [first filed, last filed or only, whichever is applicable] computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application serial number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is [included in the originally filed specification of the instant application, included in a separately filed amendment for incorporation into the specification, whichever is applicable].

Applicant is also reminded to include a statement that the CRF and the paper copy of the Sequence Listing are the same.

Applicants are required to comply with all requirements of 37 C.F.R. §§ 1.821-1.825 for all sequences listed in the present application. Any response to this Office action which fails to meet ALL of these requirements will be considered non-responsive.

Claim Objections

Claim 20 is objected to because of the following informalities: it depends from itself. In claim 21, "A n" should be --A--. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,060,305. Although the conflicting claims are not identical, they are not patentably distinct from each other because the recombinant non-toxic, non-toxigenic, non-pathogenic *Fusarium* host cell (ATCC 20334) which expresses a heterologous protein of U.S. Patent 6,060,305 is fully encompassed by claims 21 and 22. In declarations presented both in the instant and parent application (from which the above patent issued), it has been established that ATCC 20334 corresponds to *Fusarium venenatum*.

Claims 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-7 and 25-31 of U.S. Patent No. 6,180,366. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the patent are drawn to methods of producing a heterologous polypeptide in non-toxic, non-toxigenic, non-pathogenic host cells such as *Fusarium venenatum* (see for example claims 4-7) as well as to recombinant *Fusarium venenatum* cells comprising nucleic acids encoding heterologous polypeptides. Clearly, the subject matter of these claims are fully encompassed by present claims 20-22.

Claim Rejections - 35 USC § 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 20-22 are rejected under 35 U.S.C. §102(e) as being anticipated by Royer et al.

(U.S. Patent 6,180,366).

Royer et al. teach the production of a heterologous polypeptide in non-toxic, non-toxicogenic, non-pathogenic host cells such as *Fusarium venenatum* (see for example claims 4-7) as well as to recombinant *Fusarium venenatum* cells comprising nucleic acids encoding heterologous polypeptides. The host cells are rendered non-toxic, etc. by inhibiting or reducing the production of trichothecenes (mycotoxins). Preferred host cells taught by Royer et al. are *Fusarium venenatum*. Therefore, Royer et al. teach that which is recited by present claims 20-22.

This rejection may be obviated by perfecting the claim of benefit of copending, parent application 08/816,915 (see discussion above).

Claims 20-22 are rejected under 35 U.S.C. §102(a) as being anticipated by Yoder et al. (Appendix G).

Yoder et al. teach that ATCC 20344 (*F. venenatum*) has been used as a host for heterologous protein expression/production, indicating that cells comprising sequences encoding heterologous proteins were known in the art prior to Applicants' filing date. Thus, Yoder et al. teach that which is recited by the instant claims.

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This rejection may be obviated by perfecting the claim of benefit of copending, parent application 08/816,915 (see discussion above).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-22 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present claims are drawn to methods for producing a heterologous polypeptide in a non-toxic, non-toxicogenic, non-pathogenic recombinant *Fusarium* host cell and to said host cells, teleomorphs or to synonyms thereof. While the specification provides support specifically for *Fusarium venenatum* ATCC 20334 (formerly called *F. graminearum*), it does not provide an enabling disclosure for "teleomorphs or synonyms thereof" or for any *Fusarium* species other than *Fusarium venenatum* ATCC 20334. The following factors have been considered for this rejection.

The nature of the invention. The nature of the invention is predicated upon the use of the imperfect stage fungus *Fusarium* as a host for the production of heterologous proteins. There are several taxonomic schemes resulting a confused nomenclature system for *Fusarium*

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species/strains. Unclear anamorph/teleomorph (asexual and sexual stages) relationships for different *Fusarium* species/strains, the lack or undiscovered sexual stages for some species/strains of the fungus and the high variability of species/strains of the fungus in cultural and morphological characteristics all contribute to the confusion in assigning definitive names to the species/strains (see for example Yoder et al., Appendix G, page 68, second column, first paragraph) and their teleomorphs or synonyms. The highly variable nature of the host cell requires that there be a sufficient degree of certainty or accuracy in assigning species and/or strain designations to practice the full scope of the claimed invention. In addition, the nature of the cells must also include being non-toxic, non-toxigenic and non-pathogenic.

The state of the prior art and the predictability or unpredictability of the art. As discussed immediately above, the art provides different and often conflicting methodologies and outcomes for the taxonomy of *Fusarium* species/strains. In this art, there is no consistent, reliable, and accurate means for assigning definitive identities to *Fusarium* species/strains based on cultural and morphological characteristics:

Accurate identification of *Fusarium* species is problematical for both specialists and nonspecialists alike given the paucity and plasticity of morphological characters combined with discordant and often polytypic morphological species concepts employed in the three most widely used taxonomic treatment of the genus...[Appendix F, paragraph bridging pages 57 and 58].

This underlying problem also prohibits the establishment of definitive teleomorphs and synonyms.

In addition, the art teaches that several species of *Fusarium* produce mycotoxins such as zearalenones and trichothecenes. *Fusarium roseum* produces Zearalenone, commonly known as F-2 mycotoxin. *Fusarium roseum* also makes T-2 mycotoxin (a Trichothecin, see page 447 of

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Agrios). It is noted that Applicants' specification identifies *Fusarium roseum* as a synonym or teleomorph of the claimed strain of *Fusarium* (see for example page 6, line 14). At page 424, Agrios also teaches that *Gibberella zeae* (a teleomorph of the claimed *Fusarium* strain, see page 4, line 26 of the specification) causes stalk rots of corn. So it does not appear that the art recognizes or teaches teleomorphs or synonyms of the claimed *Fusarium* which are not toxigenic, toxic and pathogenic.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. At page 4, lines 24-26, the specification teaches "known teleomorphs of *Fusarium* of the section *Discolor* include, but are not limited to *Gibberella gordonii*, *Gibberella cyanea*, *Gibberella pulicaris*, and *Gibberella zeae*." Page 6, the specification further teaches:

It will be understood that throughout the specification and claims the use of the term "*Fusarium graminearum*" refers not only to organisms encompassed by this species, but also includes those species which have previously been or currently are designated as other species in alternate classification schemes, but which possess the same morphological and cultural characteristics defined above, and may be synonymous to *F. graminearum* (emphasis added). These include, but are not limited to *Fusarium roseum*, *F. roseum* var. *graminearum*, *Gibberella zeae* or *Gibberella roseum*, *Gibberella roseum* f. sp. *cerealis*."

It appears then that Applicants are using the terms "teleomorph" and "synonym"

interchangeably. Aside from providing a few examples of species or strains which are considered by Applicant to be teleomorphs or synonyms, there is no clear definition for either term (see the rejection under 35 U.S.C. § 112, second paragraph below). This contributes confusion to the already confused area of *Fusarium* taxonomy alluded to in the discussion above.

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To wit, Applicant's own initial misidentification of the strain designated as ATCC 20334 as *F. graminearum*. See also Yoder et al. (Appendix G, page 68, second column):

"Despite the fact that members of this genus represent economically important plant pathogens, identification to the species level is not always straightforward. This is because the cultural and morphological appearance of *Fusarium* strains can be highly variable depending on the cultural conditions employed and because the different taxonomic systems published for the genus (all of which are based on cultural and morphological characteristics) describe different number of sections, species and varieties."

This implies that species and strain designations based solely on cultural and/or morphological characteristics are not reliable, consistent or accurate. Applicants' misidentification of *F. venenatum* as *F. graminearum* illustrates this point and also has significant implications in terms of providing an enabling disclosure. Applicants' specification teaches what they regard as teleomorphs and synonyms for *F. graminearum*; however, the specification is completely silent with respect to teleomorphs and synonyms for *F. venenatum*. There does not appear to be any description of teleomorphs or synonyms of *F. venenatum*--which is consistent with the fact that Applicants, along with others in the field, mistook the identification of this particular species. Not only do the teleomorphs and synonyms taught in the specification appear to correspond to a completely different *Fusarium* species, they are known in the art to be toxic, toxigenic pathogenic (see above), contrary to the recited claims.

During prosecution of 08/815,915, which appears to be the immediate parent, Wendy T. Yoder provided a declaration under 37 C.F.R. §1.132 which is made of record in the present application as Appendix J accompanying a second declaration under 37 C.F.R. §1.132, also submitted by Wendy T. Yoder. In the first declaration (Appendix J), Yoder declares that *Fusarium venenatum* is the correct identification for the strain designated as ATCC 20334 and

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that this strain is the only one which fulfills the criteria for useful production strains. The criteria are set forth in pages 3-5 of Appendix J. In the studies presented, a *Fusarium* species or teleomorph thereof, *Gibberella zeae*, is assessed in terms of the criteria. Yoder unequivocally states that *F. venenatum* is the only host strain which fulfills all the criteria. Thus, the teleomorph, *Gibberella zeae* does not appear to behave or perform in the same manner as *F. venenatum* (see Appendix J, page 5, paragraph 9).

The more recent Yoder declaration (paper 3, file 16 May 2000) illustrates only *F. venenatum* strains (i.e., no teleomorph or synonym data is provided). Yoder concludes that

“the two additional wild type isolates of *F. venenatum* tested and described in this Declaration...are equivalent to or better than the *F. venenatum* strain ATCC 20334 in terms of transformation efficiency and heterologous protein production. It is also my conclusion that the *F. venenatum* strains are clearly superior to other *Fusarium* strains (emphasis added).” See page 5.

Thus, one draws the following conclusions from consideration of the two declarations and the present specification: (1) that *F. venenatum* species are the ones to use for heterologous gene expression; (2) that the non-toxic, non-toxigenic, non-pathogenic limitations of the present claims do not appear to be satisfied by teleomorphs and/or synonyms listed in the specification; and (3) that said teleomorphs and/or synonyms cannot correspond to ATCC 20334, because of misidentification of this strain as *F. graminearum*. Therefore, the specification is not enabling for teleomorphs and synonyms of *F. venenatum*. Also of note, at page 74 of Appendix G (first full sentence of column 1) it says that the teleomorphic states of several *Fusarium* species, including *venenatum*, are not known or do not exist.

The specification is not enabling for any *F. venenatum* strain other than ATCC 20334 because it fails to set forth how to identify *F. venenatum* species from other *Fusaria* and because

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this strain appears to be unique, even amongst other strains of *F. venenatum*, in its non-toxic, non-toxicogenic, and non-pathogenic nature. See for example Table 2, page 60 of Appendix F, which demonstrates that other *F. venenatum* species produce mycotoxins and the last paragraph of column 1 on page 69 of Appendix G, which indicates that ATCC 20334 is a deteriorated, pionnotal mutant. The fact that ATCC 20334 is recognized as a mutant implies that undisclosed and unspecified mutations may account for its non-toxic, non-toxicogenic, and non-pathogenic nature. The specification does not teach that other *F. venenatum* strains are non-toxic, non-toxicogenic, and non-pathogenic, in fact, the specification fails to teach any *F. venenatum* strains other than ATCC 20334, which was initially misidentified. The more recent Yoder declaration is of no help in this regard because it only demonstrates that other *F. venenatum* strains are also efficient producers of heterologous proteins, but is silent with respect to mycotoxin production and pathogenicity of these strains. Thus, the specification fails to provide adequate guidance and support for the full scope of the claimed invention.

The examiner appreciates the fact that while it may be possible to use species-specific primers to assign, with greater accuracy, correct species and strain designations to members of the section Discolor (also called *Fusarium*) using different molecular approaches, the specification fails to disclose primers specific for *F. venenatum*. The most recent Yoder declaration, again, cannot remedy this deficiency because declarations under 37 C.F.R. § 1.132 only serve to demonstrate that applications are enabled as filed. In other words, the specification would have to have disclosed the primers specific for *F. venenatum*. Clearly, this is not the case. The specification does not teach that ATCC 20344 is *F. venenatum* (but is remedied with the declarations because the strain referred to, ATCC 20334, is the same), nor does the specification

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teach how to determine if a given fungal culture is *F. venenatum*. The specification lacks teachings that are essential to practice the invention for strains of *F. venenatum* other than ATCC 20334. For these reasons, the specification fails to provide an enabling disclosure for *Fusarium* species or strains other than ATCC 20334.

The breadth of the claims and the quantity of experimentation. The claims are broadly drawn to any *Fusarium* species (see claim 20) or to different strains of *F. venenatum*, as well as to teleomorphs and synonyms thereof. As discussed above, the art did not recognize *F. venenatum* prior to Applicants' effective filing date (assuming perfection of the claim of benefit) and Applicants' own specification is drawn to a single isolate, ATCC 20334, incorrectly referred to as *F. graminearum*. Post-filing date art submitted by Applicants has established that ATCC 20334 is a *F. venenatum* strain, but the specification completely lacks the teachings necessary for the identification of *F. venenatum* strains, let alone those that are non-toxic, non-toxigenic and non-pathogenic. In the absence of these teachings, the skilled artisan would have to resort to empirical or trial and error experimentation to practice the claimed invention. This level of experimentation on the part of the skilled artisan would be undue in light of the discussion detailed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph.D. whose telephone number is (703) 305-1998. The examiner can normally be reached on Monday-Friday, 8:00am-4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be

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reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388.



Remy Yucel, Ph.D.
Primary Examiner
Art Unit 1636

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July 9, 2001